

# Scientific Opinion on the substantiation of a health claim related to SYNBIO®, a combination of Lactobacillus rhamnosus IMC 501® and Lactobacillus paracasei IMC 502®, and maintenance of normal defecation pursuant to Article 13(5) of Regulation (EC) No

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SCIENTIFIC OPINION

# Scientific Opinion on the substantiation of a health claim related to SYNBIO®, a combination of *Lactobacillus rhamnosus* IMC 501® and *Lactobacillus paracasei* IMC 502®, and maintenance of normal defecation pursuant to Article 13(5) of Regulation (EC) No 1924/2006[1]

**EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)**[2,3]

European Food Safety Authority (EFSA), Parma, Italy

## ABSTRACT

Following an application from Synbiotec S.r.l., submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Italy, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to SYNBIO®, a combination of *Lactobacillus rhamnosus* IMC 501® and *Lactobacillus paracasei* IMC 502®, and maintenance of normal defecation. The Panel considers that the food, SYNBIO®, which is the subject of the health claim, is sufficiently characterised. Maintenance of normal defecation is a beneficial physiological effect. The applicant identified three human intervention studies which investigated the effect of SYNBIO® on outcome measures (i.e. frequency of defecations, faecal bulk and stool consistency) related to the claimed effect. The Panel notes that no evidence was provided that the tools used to assess changes in bowel habits in response to an intervention were valid. Therefore, no conclusions could be drawn from these studies for the scientific substantiation of a claim on SYNBIO® and maintenance of normal defecation. In the absence of evidence for an effect of SYNBIO® on the maintenance of normal defecation in humans, studies which investigated the presence of *L. rhamnosus* IMC 501® and *L. paracasei* IMC 502® in the faeces of participants who consumed foods enriched with these strains were not considered by the Panel. The Panel concludes that a cause and effect relationship has not been established between the consumption of SYNBIO® and maintenance of normal defecation.



## KEY WORDS

SYNBIO®, *Lactobacillus rhamnosus* IMC 501®, *Lactobacillus paracasei* IMC 502®, defecation, health claims

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[1] On request from the Competent Authority of Italy following an application by Synbiotec S.r.l., Question No EFSA-Q-2014-00567, adopted on 22 April 2015.

[2] Panel members: Carlo Agostoni, Roberto Berni Canani, Susan Fairweather-Tait, Marina Heinonen, Hannu Korhonen, Sébastien La Vieille, Rosangela Marchelli, Ambroise Martin, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Sean (J.J.) Strain, Inge Tetens, Daniel Tomé, Dominique Turck and Hans Verhagen. In line with EFSA's policy on declarations of interest, Panel member Anders Sjödin did not participate in the development and adoption of this scientific output. Correspondence: nda@efsa.europa.eu

[3] Acknowledgement: The Panel wishes to thank the members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Marina Heinonen, Ambroise Martin, Hildegard Przyrembel, Yolanda Sanz, Alfonso Siani, Sean (J.J.) Strain, Inge Tetens, Hendrik Van Loveren, Hans Verhagen and Peter Willatts, for the preparatory work on this scientific opinion.

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## SUMMARY

Following an application from Synbiotec S.r.l., submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Italy, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to SYNBIO®, a combination of *Lactobacillus rhamnosus* IMC 501® and *Lactobacillus paracasei* IMC 502®, and maintenance of normal defecation.

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The application included a request for the protection of proprietary data.

The food that is the subject of the health claim is SYNBIO®, a combination (1:1) of two bacterial strains, *Lactobacillus rhamnosus* IMC 501® and *Lactobacillus paracasei* IMC 502®. SYNBIO® is available in the form of a lyophilised powder to be added to foods or used as a dietary supplement. The identification and characterisation of the strains at species and strain levels have been performed by applying appropriate phenotypic and genotypic methods. The Panel considers that the food, SYNBIO®, which is the subject of the health claim, is sufficiently characterised.

The claimed effect proposed by the applicant is "favouring the natural regularity and contributing to maintain and improve human intestinal well-being". The target population proposed by the applicant is the healthy adult population. Upon a request by EFSA for clarification of the claimed effect, the applicant indicated that the claimed effect is maintenance of normal defecation and the outcome measures to substantiate the claimed effect were "intestinal regularity" (i.e. stool frequency), stool volume and stool consistency. The Panel considers that maintenance of normal defecation is a beneficial physiological effect.

The applicant identified three human intervention studies which investigated the effect of SYNBIO® on outcome measures (i.e. frequency of defecations, faecal bulk and stool consistency) related to the claimed effect.

In these double-blind, placebo-controlled parallel intervention studies, healthy adults were randomised to consume daily food portions enriched with SYNBIO® or capsules of SYNBIO® or their corresponding placebos (same food or capsules without SYNBIO®) for 12 weeks.

In these studies, participants were asked to record daily the number of defecations and the number of "stool eggs" (used as a surrogate measure for stool volume). In two of the three studies, participants were also asked to assess daily stool consistency using the Bristol Stool Scale. At the end of each study period, participants were asked to self-evaluate how their bowel habits had changed, compared with the period before the interventions, by completing questionnaires which were based on Likert scales. In one study, a questionnaire based on a Bristol Stool Scale was used by the participants to self-evaluate changes in stool consistency at the end of the study period. Only results of the statistical analyses of the Likert scale scores and the Bristol Stool Scale values (in one study), which were obtained at the end of the study periods, were provided.

The Panel notes that no evidence was provided by the applicant that the Likert scales or the Bristol Stool Scale, as used in the three studies mentioned above, are valid tools for assessing changes in bowel habits in response to an intervention (i.e. on their ability to yield consistent and reproducible estimates of changes in bowel habits over time), and thus it is unclear how the outcome measures derived from these assessments relate to the claimed effect (i.e. maintenance of normal defecation).

The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of a claim on SYNBIO® and maintenance of normal defecation.

In the absence of evidence for an effect of SYNBIO® on the maintenance of normal defecation in humans, studies which investigated the presence of *L. rhamnosus* IMC 501® and *L. paracasei* IMC 502® in the faeces of participants who consumed foods enriched with these strains were not considered by the Panel.

The Panel concludes that a cause and effect relationship has not been established between the consumption of SYNBIO®, a combination of *Lactobacillus rhamnosus* IMC 501® and *Lactobacillus paracasei* IMC 502®, and maintenance of normal defecation.

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## BACKGROUND

Regulation (EC) No 1924/2006[4] harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation, and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Article 13(5) of this Regulation lays down provisions for the addition of claims (other than those referring to the reduction of disease risk and to children's development and health) which are based on newly developed scientific evidence, or which include a request for the protection of proprietary data, to the Community list of permitted claims referred to in Article 13(3).

According to Article 18 of this Regulation, an application for inclusion in the Community list of permitted claims referred to in Article 13(3) shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

## STEPS TAKEN BY EFSA

- The application was received on 06/08/2014.
- The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The application included a request for the protection of proprietary data.
- On 11/09/2014, during the validation process of the application, EFSA sent a request to the applicant to provide missing information.
- On 26/09/2014, EFSA received the missing information as submitted by the applicant.
- The scientific evaluation procedure started on 31/10/2014.
- On 26/11/2014, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application. The scientific evaluation was suspended on 09/12/2014 and was restarted on 24/12/2014, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
- On 05/01/2015, EFSA received the requested information (which was made available to EFSA in electronic format on 30/12/2014).
- On 06/02/2015, the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application. The scientific evaluation was suspended on 11/02/2015, in compliance with Article 18(3) of Regulation (EC) No 1924/2006. On 26/02/2015, EFSA received the requested information and the scientific evaluation was restarted.
- During its meeting on 22/04/2015, the NDA Panel, having evaluated the data, adopted an opinion on the scientific substantiation of a health claim related to SYNBIO®, a combination of *Lactobacillus rhamnosus* IMC 501® and *Lactobacillus paracasei* IMC 502®, and maintenance of normal defecation.

## TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16(3) of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an

[4] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

opinion on the scientific substantiation of a health claim related to: SYNBIO®, a combination of *Lactobacillus rhamnosus* IMC 501® and *Lactobacillus paracasei* IMC 502®, and maintenance of normal defecation.

## EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of SYNBIO®, a combination of *Lactobacillus rhamnosus* IMC 501® and *Lactobacillus paracasei* IMC 502®, a positive assessment of its safety, nor a decision on whether SYNBIO® is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wording of the claim, and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 18(4) of Regulation (EC) No 1924/2006.

## INFORMATION PROVIDED BY THE APPLICANT

### Applicant's name and address

Synbiotec S.r.l. Via Gentile III da Varano, 62032, Camerino (MC), Italy.

The application includes a request for the protection of proprietary data for the two bacterial strains and some information pertaining to their characterisation, in accordance with Article 21 of Regulation (EC) No 1924/2006.

### Food/constituent as stated by the applicant

According to the applicant, SYNBIO® is a combination (1:1) of two probiotic bacterial strains *Lactobacillus rhamnosus* IMC 501® and *Lactobacillus paracasei* IMC 502®, in the form of a lyophilised powder to be added to functional foods or used, alone or in combination with other ingredients, as a dietary supplement.

### Health relationship as claimed by the applicant

According to the applicant, by consuming probiotic functional foods enriched with SYNBIO® or dietary supplements composed of SYNBIO®, consumers will obtain the effect of a persistence of two probiotic bacterial strains *Lactobacillus rhamnosus* IMC 501® and *Lactobacillus paracasei* IMC 502®, in the intestinal tract which will favour natural regularity and contribute to maintaining and improving human intestinal well-being. The primary outcome measures used were intestinal regularity and increased stool volume.

### Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: "SYNBIO® persists in the intestinal tract and favours the natural regularity contributing to maintain and improve human intestinal well-being".

### Specific conditions of use as proposed by the applicant

The target population proposed by the applicant is the healthy adult population.

The applicant has proposed a daily intake of SYNBIO® of at least $10^9$ colony-forming units (CFU). This can be obtained by consuming foods (i.e. yoghurt, "ricotta" cheese, "mozzarella" cheese, chocolate, chocolate mousse or ice-cream) containing at least $10^9$ CFU of SYNBIO® per 100 g of food, or capsules containing at least $10^9$ CFU.

## ASSESSMENT

### 1. Characterisation of the food/constituent

The food that is the subject of the health claim is SYNBIO®, a combination (1:1) of two bacterial strains, *Lactobacillus rhamnosus* IMC 501® and *Lactobacillus paracasei* IMC 502®. SYNBIO® is available in the form of a lyophilised powder to be added to foods or used as a dietary supplement. The two bacterial strains, *Lactobacillus rhamnosus* IMC 501® and *Lactobacillus paracasei* IMC 502®, were isolated from the faeces of healthy elderly people (Silvi et al., 2003). The strains were identified and characterised by applying appropriate phenotypic and genotypic methods. The genotypic methods applied included sequence analysis of the 16S rRNA gene and RAPD analysis for

species and strain identification, respectively (Verdenelli et al., 2009). The characterisation of the strains has also been published in patents (Cresci et al., 2004, 2005) and it is also described in an unpublished PhD thesis (Verdenelli, 2007).

The strains were deposited in the DSMZ (Deutsche Sammlung von Mikroorganismen und Zellkulturen) culture collection, Germany, and have the following deposition numbers: DSM 16104 and DSM 16105. The DSMZ has been nominated as an International Depositary Authority under the Budapest Treaty.

The applicant provided data on the stability of the strains and their effects on the chemical-physical and organoleptic parameters of the foods (i.e. ice-cream, chocolate mousse, chocolate bars, mozzarella, ricotta and yoghurt) to which they were added.

The Panel considers that the food, SYNBIO®, a combination of *Lactobacillus rhamnosus* IMC 501® and *Lactobacillus paracasei* IMC 502®, which is the subject of the health claim, is sufficiently characterised.

## 2. Relevance of the claimed effect to human health

The claimed effect proposed by the applicant is "favouring the natural regularity and contributing to maintain and improve human intestinal well-being". The target population proposed by the applicant is the healthy adult population.

Upon a request by EFSA for clarification of the claimed effect, the applicant indicated that the claimed effect is maintenance of normal defecation and the outcome measures to substantiate the claimed effect were "intestinal regularity" (i.e. stool frequency), stool volume and stool consistency.

Constipation is associated with less frequent defecations, with reduced faecal bulk and/or harder stools, or both. Constipation leads to gastrointestinal discomfort and may contribute to the development of, for example, diverticular disease. More frequent defecations through, for example, a reduction in transit time, increased faecal bulk and softer stools, may contribute to the maintenance of normal defecation, provided that this does not result in diarrhoea.

The Panel considers that maintenance of normal defecation is a beneficial physiological effect.

## 3. Scientific substantiation of the claimed effect

The applicant performed a literature search in PubMed, Scopus and ISI Web of Knowledge using, as search terms, "*Lactobacillus rhamnosus* IMC 501", "*Lactobacillus paracasei* IMC 502" and "SYNBIO" to identify pertinent human data. Publications related to strains other than *Lactobacillus rhamnosus* IMC 501 and *Lactobacillus paracasei* IMC 502, as well as those not related to bowel habits or bowel function, were excluded.

The applicant identified three human intervention studies which investigated the effect of SYNBIO® on outcome measures (i.e. frequency of defecations, faecal bulk and stool consistency) related to the claimed effect (Verdenelli et al., 2011a, b; Silvi et al., 2014).

In the double-blind, placebo-controlled parallel intervention study by Verdenelli et al. (2011a), 50 healthy adults (aged 23–65 years, 27 females) were randomised to consume daily at least one food portion (80–120 g of yoghurt, "ricotta" cheese, "mozzarella" cheese, chocolate, chocolate mousse or ice-cream) enriched with SYNBIO® (about $10^9$ CFU per serving; n = 25) or placebo (same food without SYNBIO®; n = 25) for 12 weeks.

Upon a request by EFSA for clarification of the outcome measures assessed in the study and the methods of measurement, the applicant indicated that the primary outcome measures were "intestinal regularity" (i.e. stool frequency) and stool volume, which were recorded daily by the participants as the number of defecations (i.e. stool frequency) and the number of "stool eggs" (used as a surrogate measure for stool volume). At the end of the study, participants were also asked to self-evaluate how stool frequency and stool volume had changed, compared with the period before the intervention, by completing a questionnaire which used a Likert scale. Only the statistical analysis of the Likert scale scores, which were obtained at the end of the study, was provided. The Panel notes that changes in stool frequency and stool volume from baseline, using data recorded daily by the participants, were not reported.

In the double-blind, placebo-controlled, parallel intervention study by Verdenelli et al. (2011b) 160 amateur male cyclists (aged 27–43 years) were randomised to consume daily one capsule of SYNBIO® (about $10^9$ CFU/capsule; n = 80) or placebo (maltodextrin; n = 80) for 12 weeks.

Upon a request by EFSA for clarification of the outcome measures assessed in the study and the methods of measurement, the applicant indicated that stool frequency, stool volume, stool consistency and cold symptoms were the primary outcomes of this study. Ease of defecation, borborygmi/rumbling stomach, bloating, flatulence, constipation, diarrhoea, abdominal pain and intestinal cramps were among the secondary outcome measures investigated in the study. Participants were asked to record daily the number of defecations and the number of "stool eggs" of an approximated size represented in a graph (used as a surrogate measure for stool volume). Stool consistency was assessed daily by the participants using the Bristol Stool Scale. At the end of the study, participants were also asked to self-evaluate how stool frequency, stool volume and stool consistency had changed, compared with the period before the intervention, by completing a questionnaire which used a Likert scale. Only the statistical analysis of the Likert scale scores, which were obtained at the end of the study, was provided. The Panel notes that changes in stool frequency, stool volume and stool consistency from baseline, using data recorded daily by participants, were not reported.

In the double-blind, placebo-controlled, parallel intervention study by Silvi et al. (2014), 862 healthy adults (aged 18–65 years, 470 females) were randomised to consume daily at least one food portion (80–120 g) enriched with SYNBIO® (about $10^9$ CFU per serving; n = 217), one capsule of SYNBIO® (about $10^9$ CFU/capsule; n = 213), or their corresponding placebos (i.e. same food or capsules without SYNBIO®; n = 213 in the placebo food group and n = 219 in the placebo capsule group) for 12 weeks.

Upon a request by EFSA for clarification of the outcome measures assessed in the study and the methods of measurement, the applicant indicated that stool frequency and stool volume were the primary outcomes of this study, whereas stool consistency was a secondary outcome. Participants were asked to record daily the number of defecations and the number of "stool eggs" of an approximated size represented in a graph (used as a surrogate measure for stool volume). Stool consistency was assessed daily by the participants using the Bristol Stool Scale. At the end of the study, participants were asked to self-evaluate how stool frequency and stool volume had changed, compared with the period before the intervention, by completing a questionnaire which used a Likert scale. At the end of the study, participants were also asked to self-evaluate changes in stool consistency by using the Bristol Stool Scale. A comparison of "mean values" of the Bristol Stool Scale between groups was presented in the statistical analysis. Upon a request by EFSA for clarification on how the "mean values" of the Bristol Stool Scale were calculated, the applicant indicated that "mean values" for each group were calculated from the single values obtained in each subject at the end of the study period. Only the statistical analyses of the Likert scale scores (stool frequency and stool volume) and the Bristol Stool Scale (stool consistency) values obtained at the end of the study were provided. The Panel notes that changes in stool frequency, stool volume and stool consistency from baseline, using data recorded daily by the participants, were not reported.

In relation to the studies described above (Verdenelli et al., 2011a, b; Silvi et al., 2014), EFSA requested the applicant to clarify whether the Likert-scale-based questionnaires and the Bristol Stool Scale, as used in these studies, were validated to assess changes in bowel habits over time. No information was provided by the applicant on how these scales, as used, were validated to quantify changes in stool frequency, stool volume and/or stool consistency over time.

EFSA also requested the applicant to clarify the reason for not using the data (i.e. number of defecations, number of "stool eggs" and stool consistency) recorded daily by the participants to assess changes in bowel habits over time. The applicant indicated that "the interest of the study was to assess whether the participants felt better or worse at the end of the intervention, and did not want to know the daily change".

The Panel notes that no evidence was provided by the applicant that the Likert scales or the Bristol Stool Scale, as used in the studies above, are valid tools for assessing changes in bowel habits in response to an intervention (i.e. on their ability to yield consistent and reproducible estimates of changes in bowel habits over time), and thus it is unclear how the outcome measures derived from these assessments relate to the claimed effect (i.e. maintenance of normal defecation).

The Panel also notes that inadequate information was provided on how power calculations were performed in two of the studies (Verdenelli et al., 2011a, b).

The Panel considers that no conclusions can be drawn from the three studies described above for the scientific substantiation of a claim on SYNBIO® and maintenance of normal defecation.

In the absence of evidence for an effect of SYNBIO® on the maintenance of normal defecation in humans, studies which investigated the presence of *L. rhamnosus* IMC 501® and *L. paracasei* IMC 502® in the faeces of participants who consumed foods enriched with these strains were not considered by the Panel (Silvi et al., 2003; Cresci et al., 2004, 2005; Verdenelli et al., 2007, 2009).

The Panel concludes that a cause and effect relationship has not been established between the consumption of SYNBIO®, a combination of *Lactobacillus rhamnosus* IMC 501® and *Lactobacillus paracasei* IMC 502®, and maintenance of normal defecation.

## CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food, SYNBIO®, a combination of *Lactobacillus rhamnosus* IMC 501® and *Lactobacillus paracasei* IMC 502®, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect proposed by the applicant is "favouring the natural regularity and contributing to maintain and improve human intestinal well-being". The target population proposed by the applicant is the healthy adult population. Maintenance of normal defecation is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of SYNBIO®, a combination of *Lactobacillus rhamnosus* IMC 501® and *Lactobacillus paracasei* IMC 502®, and maintenance of normal defecation.

## DOCUMENTATION PROVIDED TO EFSA

1. Health claim application on SYNBIO®, a combination of *Lactobacillus rhamnosus* IMC 501® and *Lactobacillus paracasei* IMC 502®, and maintenance of normal defecation pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0425_IT). August 2014. Submitted by Synbiotec S.r.l.

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## ABBREVIATIONS

| | |
|---|---|
| CFU | colony-forming unit |
| DSMZ | Deutsche Sammlung von Mikroorganismen und Zellkulturen |